REMARKS

The final Official Action dated October 23, 2006 and the Advisory Action dated March 1, 2007 have been carefully considered. Accordingly, the amendments presented herewith, taken with the Amendment filed January 23, 2007 and the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present amendment, new claims 22-24 are added. Support for these claims may be found through out the specification. It is believed that this amendment does not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 1-5, 10, 13 and 17-19 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner asserted that the claims have no written support in the specification for the broad genus "LPS derived from microbial and/or fungal endotoxin," but only have support for "LPS derived from *E. coli* bacteria".

Applicants traverse this rejection. However, to expedite prosecution of this application, claim 1 was previously amended to delete the words "microbial and/or fungal" and add the word "bacterial", in accordance with the teachings of the specification at page 4, line 16 and page 5, lines 4-8. In addition, Applicants submit that *E. coli* bacteria exemplified in the specification is a representative species of the genus of LPS derived from bacterial endotoxins as recited in claim 1. Trent, "Biosynthesis, transport, and modification of lipid A", *Biochem Cell Biol.* 2004 Feb; 82(1):71-86 discloses that gram-negative bacteria in general have very similar LPS structural properties. A copy of the Trent reference was previously submitted with the Amendment filed with the U.S. Patent and Trademark Office on July 24, 2006. Thus, the present specification disclosure of bacterial endotoxin is sufficiently described within the meaning of 35 U.S. C. §112, first paragraph. Accordingly, it is therefore submitted that the evidence previously presented demonstrates that the specification's disclosure of LPS derived from *E. coli* bacteria provides sufficient support for the genus of LPS derived from bacterial endotoxin and the rejection is overcome. Reconsideration is respectfully requested.

Claims 1-5, 10, 13 and 17-19 were rejected under 35 U.S.C. §103(a) as being obvious and therefore unpatentable over Tulic et al, *Am. J. Resp. Cell Mol. Biol.*, Vol. 22, pp. 604-612, 2000

in view of Matricardi et al, "Microbial Products in Allergy Prevention and Therapy", *Allergy*, 2003:58:pp. 461-471, Bertók, "Stimulation of Nonspecific Resistance By Radiation-Detoxified Endotoxin", *Beneficial Effects of Endotoxins*, Plenum Publishing Corp., 1983, pp. 213-226, and Liu et al, *Current Reviews of Allergy and Clinical Immunology*, Vol. 109, pp. 379-392, 2002. The Examiner asserted that Tulic et al teach the prevention of allergy in young adult 8-10 week old rats administered LPS in aerosol; however, the Examiner acknowledges that Tulic et al fail to teach the administration of irradiated LPS to neonatal mammals. The Examiner asserted that Matricardi et al teach that the administration of native LPS is beneficial to treat allergy, however, a less toxic derivative of native LPS would be preferred for treatment purposes due to the severe endotoxic effects of native LPS. The Examiner asserted that Bertók teaches the use of detoxified LPS to induce tolerance to toxic effects and to mobilize the host defenses in an immunologically nonspecific fashion, but fails to teach the type of immune response stimulated by the irradiated LPS. The Examiner asserted that Liu et al teach that there is ample data demonstrating that exposure to endotoxins, such as LPS, in early life, less than two years, has been demonstrated to decrease allergic sensitization; and that frequent benign exposures to endotoxin early in life should be expected to influence immune development to prevent atopy, allergic disease and asthma. Accordingly, the Examiner asserted that one of ordinary skill in the art would have been motivated to treat the young adult 8-10 week old rats of Tulic et al with the irradiated LPS molecules of Bertók because the irradiated LPS molecules are immunostimulatory, less toxic derivatives of LPS, Matricardi et al having taught that a less toxic derivative of LPS is preferred for the treatment of allergy. The Examiner further asserted that one of ordinary skill in the art would have been motivated to treat young humans with the teachings of Matricardi et al, Tulic et al and Bertók, since Liu et al recognize that early benign exposure to native LPS can be effective in preventing allergy.

In the Advisory Action dated March 1, 2007, the Examiner also asserted that the newly cited Lin et al, "The association between lung innate immunity and differential airway antigen-specific immune responses," *In. Immunol.* 8(4): 499-507, 1996, teach that the specific immune response to an airway antigen is dependent upon the innate nonspecific immune response and controls whether a Th1 or Th2 response is generated in mice. Accordingly, the Examiner asserted that one of ordinary skill in the art would have known that the nonspecific resistance induced by radiation-detoxified LPS could be applied to inhibit allergic disease because it had been shown that the specific immune response to airway allergen was determined by the nonspecific immune response to LPS.

However, as will be set forth in detail below, Applicants submit that the processes defined by claims 1-5, 10, 13 and 17-19 are nonobvious over and patentably distinguishable from Tulic et al in view of Matricardi et al, Liu et al, and Bertók, even in further view of Lin et al cited in the Advisory Action. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Particularly, claim 1 recites a process for inhibiting development of allergic disease. The process comprises exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide derived from bacterial endotoxin.

New claim 22 recites a process for inhibiting development of allergic disease. The process comprises exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide derived from E. coli bacteria endotoxin.

Applicants submit that the combination of references does not teach, suggest or recognize the use of irradiated-LPS in a neonatal or immature mammal or bird for inhibiting the development of allergic disease.

As set forth in the Amendment under 37 C.F.R. 1.116 dated January 23, 2007, Tulic et al teach the prevention of allergy in young adult (8-10 week old) rats administered native LPS in aerosol. In contrast, the present claims are directed to processes for inhibiting development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide. As noted by the Examiner, Tulic et al fail to teach, suggest or recognize the administration of irradiated LPS. In addition, Applicants submit that Tulic et al also fail to teach, suggest or recognize the administration of irradiated LPS to a neonatal or immature mammal or bird. The specification of the present invention at page 2, lines 23-25 defines "immature" as a mammal or bird which has not completed life cycle development to its adult stage. The 8-10 week old rats in Tulic et al are not considered immature as defined by the present application because they have completed life cycle development to their adult stage as rats can reach breeding maturity, i.e., adult stage, at 6 weeks of age. *See <<health.ratzrus.co.uk/breeding.htm>>*, which reference was previously submitted in the Amendment under 37 C.F.R. 1.116 dated January 23, 2007. Accordingly, Tulic et al teach the administration of native LPS to adult rats. As Tulic et ail fail to teach use of irradiation-detoxified LPS and fail to teach treatment of neonatal or immature subjects, Tulic et al do not teach, suggest or recognize processes for inhibiting the development of allergic disease

comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide as required by the present claims.

The deficiencies of Tulic et al are not overcome by the teachings of Matricardi et al. As set forth in the Amendment under 37 C.F.R. 1.116 dated January 23, 2007, Matricardi et al also fail to teach the use of irradiation-detoxified LPS and fail to teach treatment of a neonatal or immature mammal or bird as required by the claims. Matricardi et al merely hypothesize that the administration of native LPS may stimulate an immune response to treat allergy in human (adult) volunteers. However, Matricardi et al disclose that the potential use of native LPS as a therapeutic agent is limited because of its severe endotoxic effects. See pages 467-468. Accordingly, Matricardi et al conclude that the use Monophosphoryl Lipid A (MPL) is of interest over native LPS because Monophosphoryl Lipid A (MPL) has similar potent adjuvant properties of native LPS, but is less toxic. Not only does Matricardi fail to teach, suggest or recognize the exposure of irradiation-detoxified LPS to a neonatal or immature mammal or bird to inhibit the development of allergic disease, the disclosures of Matricardi et al appear to teach away from the claimed invention in teaching that LPS is limited in its potential use as a therapeutic agent to treat allergy because of its severe endotoxic effects. It is error to find obviousness when a reference diverges from and teaches away from the invention at hand, *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

The Examiner asserts that since Matricardi et al disclose that native LPS has toxic effect, Matricardi et al suggest the use of irradiated LPS. However, Matricardi et al provide no such suggestion, rather suggest MPL in place of native LPS. Only hindsight review of the present application can lead to a finding of a suggestion of irradiated LPS in the teachings of Matricardi et al. Therefore, Matricardi et al do not teach, suggest or recognize use of irradiation-detoxified LPS or treatment of neonatal or immature subject and therefore do not resolve the deficiencies of Tulic et al.

The deficiencies of Tulic et al and Matricardi et al are not overcome by the teachings of Liu et al. As set forth in the Amendment under 37 C.F.R. 1.116 dated January 23, 2007, Liu et al disclose a review of studies on endotoxin exposure. However, Liu et al fail to teach, suggest or recognize the use of irradiation detoxified LPS or any treatment for inhibiting the development of allergic disease in a neonatal or an immature mammal or bird. Liu et al on page 385 disclose "challenge studies with different samples of cotton dust demonstrated that the endotoxin content

of the cotton dust, and not the dust exposure itself, correlated with induced airflow obstruction. Since then, endotoxin exposure has been associated with respiratory symptoms and disease in a long list of workplace settings (e.g., livestock handling, lab animal handling, grain and vegetable agriculture, sawmills, waste management, fiberglass manufacturing, and sick building syndrome)". Accordingly, while Liu et al recognize that endotoxins can have both beneficial and detrimental effects regarding prevention or development of allergies and asthma, Liu et al do not teach, suggest or recognize that modification of endotoxin through irradiation, or any other chemical modifications for that matter, might yield a more beneficial and less detrimental product, nor do Liu et al teach or suggest a method for treatment of a neonatal or immature subject. Therefore, as with Tulic et al and Matricardi et al, Liu et al fail to teach, suggest or recognize the processes of exposing a neonatal or an immature mammal or bird to irradiation detoxified LPS to inhibit the development of allergic disease.

The deficiencies of Tulic et al, Matricardi et al and Liu et al are not overcome by the teachings of Bertók. As set forth in the Amendment under 37 C.F.R. 1.116 dated January 23, 2007, Bertók discloses the use of detoxified LPS to induce a nonspecific resistance in the pretreatment of various shocks, radiation diseases and infections. While Bertók teaches detoxified LPS, the uses thereof disclosed by Bertók are significantly distinguishable from those of the primary reference, Tulic et al and from the methods presently claimed. More specifically, the Bertók reference discloses radiation-detoxified endotoxins, i.e., LPS, may be used to stimulate a nonspecific resistance for the pretreatment in various shocks, radiation disease and infections. A nonspecific resistance is a defense mechanism that provides a systemic response to a variety of pathogens, i.e., shocks, radiation disease and infections, without distinguishing one pathogen from another. This general response prevents the pathogen(s) from either entering the body or inhibits the spread of the pathogen(s) after entering the body. However, Bertók fails to teach, suggest or recognize that irradiated-LPS may be used to induce a specific resistance to inhibit the development of allergic disease, particularly in a neonatal or immature mammal or bird by stimulating an immune response. Therefore, one of ordinary skill in the art would not be motivated to look at the teachings of Bertók to inhibit the development of allergic disease, particularly in a neonatal immature mammal or bird, notwithstanding Bertók's use of detoxified LPS.

In contrast, the administration of irradiation-detoxified LPS to a neonatal or immature mammal or bird, as defined by the present invention, induces a specific resistance to thereby

inhibit the development of an allergic disease. A specific resistance does not provide a non-distinguishing systemic response to a pathogen but, in contrast, stimulates the immune system to respond to the specific pathogen. As disclosed at page 4, line 15 - page 5, line 8 of the present specification, the administration of irradiation-detoxified LPS induces a specific resistance stimulating the Th-1 arm of the immune system to inhibit the development of an allergic disease in a neonatal or immature mammal or bird. None of the cited references teach, suggest or recognize such a method. In fact, Applicants find no suggestion in any of the references, and the Examiner has not cited any suggestion of treatment of neonatal or immature subjects as recited in the present claims. Thus, the cited references simply fail to render the claimed methods obvious.

To further evidence that one skilled in the art would not be motivated to look at the teachings of the Bertók reference to inhibit the development of allergic disease in a neonatal or immature mammal or bird, Applicants submitted the Declaration of Dr. Lóránd Bertók with the Amendment under 37 C.F.R. 1.116 dated January 23, 2007. As set forth in the Advisory Action dated March 1, 2007, the Declaration of Dr. Bertók was entered.

According to paragraph 3 of Dr. Bertók's Declaration, based on his experience in the medical and research fields, and particularly the field of immunology, it is his opinion that there is no teaching, suggestion or reference in the cited Bertók reference to use irradiation detoxified LPS to inhibit the development of allergic disease in a neonatal or immature mammal or bird. Specifically, based on his extensive experience in the field of immunology, it is his opinion the use of irradiation detoxified LPS to induce a nonspecific resistance for the pretreatment of various shocks, radiation disease and infections does not teach, suggest or recognize the use of irradiation detoxified LPS to stimulate a specific response to inhibit the development of allergic disease in a neonatal or immature mammal or bird. Moreover, it is his opinion that there would be no motivation to look to the teachings of the Bertók reference to inhibit the development of allergic disease in a neonatal or immature mammal or bird because the Bertók reference is directed to the stimulation of a nonspecific resistance, while the claimed processes of the present invention induce a specific resistance to stimulate a Th-1 immune response to inhibit the development of allergic disease in a neonatal or immature mammal or bird. One of ordinary skill in the art would, in his opinion, have no expectation that a pathogen providing the nonspecific resistance taught by the Bertók reference would be suitable for providing a different, specific resistance to inhibit the development of allergic disease in a neonatal or immature mammal or bird. Accordingly, based on his experience, it is his opinion that there would be no teaching,

suggestion or motivation to combine the Bertók reference with the other cited references because the Bertók reference specifically teaches the use of irradiation detoxified endotoxin to induce an elevated nonspecific resistance for the pretreatment of various shocks, radiation disease and infections.

Therefore, Applicants submit that the claimed processes of inhibiting the development of allergic disease by exposing a neonatal or immature mammal or bird to a radiation detoxified lipopolysaccharide derived from microbial endotoxin, which induces a specific resistance stimulating the Th-1 immune response, are not obvious to one of ordinary skill in the art over the cited combination of references.

The Federal Circuit has held that "[w]hen a rejection depends on a combination of prior art references; there must be some teaching, suggestion, or motivation to combine the references." *In re Rouffet*, 149 F.3d 1350, 13556 (Fed. Cir. 1998) (citing *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987)). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination." *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). The Examiner must give some reason as to why one of ordinary skill in the art would have been prompted to combine the teachings of the cited references to arrive at the claimed invention since it is the burden of the Examiner to establish a *prima facie* case of obviousness. The Examiner cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention; the Examiner has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination, *Smith-Kline Diagnostics, Inc. v. Helena Laboratories Corp.*, 8 U.S.P.Q. 2d 1468, 1475 (Fed. Cir. 1988). Finally, both a suggestion to combine the references and a reasonable expectation of success must be found in the art itself for a proper prima facie case of obviousness, *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Because the use of irradiation-detoxified LPS in the disclosures of the Bertók reference stimulate a nonspecific response for the pretreatment of various shocks, radiation disease and infections, one skilled in the art would not be motivated to look to the disclosures of the Bertók reference to induce a specific resistance to inhibit the development of allergic disease in a neonatal of immature mammal or bird.

In response to Applicants arguments and the Declaration of Dr. Bertók filed with the Amendment under 37 CFR 1.116, the Examiner asserted that such arguments and the Declaration

are not persuasive. Applicants note that opinion testimony is entitled to consideration and weight as long as the opinion is not on the ultimate legal conclusion at issue, MPEP §716, and opinion testimony regarding what the prior art taught may be entitled to considerable deference, *In re Carroll*, 202 U.S.P.Q. 571 (CCPA 1979). From the statements made by the Examiner in the Advisory Action of March 1, 2007, it appears that the Examiner did not consider or give any weight to the Declaration of Dr. Bertók. The Declaration was previously submitted to further evidence that one skilled in the art would not be motivated to look at the teachings of the Bertók reference to inhibit the development of allergic disease in a neonatal or immature mammal or bird. The Examiner's lack of attention to the Declaration demonstrates that it was not properly considered.

Further, in the Advisory Action, the Examiner asserted a new reference, Lin et al, for teaching that the specific immune response to an airway antigen is dependent upon the innate nonspecific immune response and controls whether a Th1 or Th2 response is generated in mice. Accordingly, the Examiner asserted that one of ordinary skill in the art would have known that a nonspecific resistance induced by radiation-detoxified LPS could be applied to inhibit allergic disease because it had been shown that the specific immune response to airway allergen was determined by the nonspecific immune response to LPS.

Initially, Applicants noted that Lin et al, like all of the other references relied upon by the Examiner fail to teach the use of irradiation-detoxified LPS in the treatment of neonatal or immature subjects. Moreover, as set forth in the Abstract of the Lin et al reference, Lin et al teach that after exposure to native LPS, mice with different genotypes produce different immune responses. Specifically, in cells of BALB/cJ strain mice (mice carrying the H-2d genotype), the IL-12 mRNA expression (Th-1 immune response) was higher while in cells of C57BL/6J strain mice (mice carrying the H-2d genotype), the IL-10 and prostaglandin E2 expression (Th-2 immune response) was higher. Lin et al also disclose the exposure of other antigens, such as ovalbumin (OVA) antigen, to the different genotypic mice models to determine the immune response generated for each genotype. Accordingly, the teachings of Lin et al are directed to how different genotypes in mice influence an immune response when exposed to the same antigen. Therefore, one skilled in the art would not be motivated to look to the teachings of the Lin et al reference to combine with the teachings of Tulic et al, Matricardi et al, Liu et al or Bertók because these references are directed to the effect of LPS on an individual irrespective of the individual's genotype.

Accordingly, the Examiner's assertion that it is prima face obvious to combine the teachings of Lin et al with the teachings of Bertók, Tulic, Matricardi et al or Liu et al, particularly to arrive at the present invention, is "hindsight reconstruction or, at best...obvious to try", *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (CAFC 1987). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination." *Id.* The Examiner must give some reason as to why one of ordinary skill in the art would have been prompted to combine the teachings of the cited references to arrive at the claimed invention since it is the burden of the Examiner to establish a *prima facie* case of obviousness. The Examiner cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention; the Examiner has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination, *Smith-Kline Diagnostics, Inc. v. Helena Laboratories Corp.*, 8 U.S.P.Q. 2d 1468, 1475 (Fed. Cir. 1988). The requisite teaching or suggestion is simply not present in the Examiner's combination.

Further, references relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). As noted above, Applicants find no teaching, suggestion or reference in Tulic et al in view of Matricardi et al, Liu et al, Bertók and Lin et al of processes for inhibiting development of allergic disease comprising exposing a neonatal or immature mammal or bird to irradiation-detoxified lipopolysaccharide derived from bacterial endotoxin as recited by the present claims. In addition, Applicants find no teaching, suggestion or reference in Tulic et al in view of Matricardi et al, Liu et al, Bertók and Lin et al for modifying the disclosures therein to arrive at the claimed invention. In view of the failure of Tulic et al in view of Matricardi et al, Liu et al, Bertók and Lin et al to teach, suggest or recognize processes for inhibiting the development of allergic disease by exposing a neonatal or immature mammal or bird to irradiation detoxified lipopolysaccharide derived from bacterial endotoxin as recited by the claims, the references do not support a rejection of claims 1-5, 10, 13 and 17-19 under 35 U.S.C. §103. It is therefore submitted that the claimed processes as defined by claims 1-5, 10, 13 and 17-19 are nonobvious over and patentably distinguishable from the teachings of Tulic et al in view of Matricardi et al, Liu et al, Bertók and Lin et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejection of the claims under 35 U.S.C. §§103 and 112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

By: _____

Clare M. Tery
Registration No. 51,833
Attorney for Applicant(s)
DINSMORE & SHOHL LLP
1900 Chemed Center
255 East Fifth Street
Cincinnati, Ohio 45202
(513) 977-8683

1352413